

Rheumatology and musculoskeletal medicine

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Summary

MUSCULOSKELETAL disease accounts for a large proportion of a general practitioner's (GP's) workload. Proper management can not only improve quality of care, but also increase job satisfaction and reap rewards under the new contract.

Osteoporosis creates a huge socioeconomic burden of disease and disability. Identifying high-risk groups in primary care and using preventative treatment can result in a substantial reduction in morbidity and mortality. GPs can help by presenting a unified lifestyle message, advising on fall prevention, and providing effective treatment; in particular, calcium and vitamin D for female nursing home residents.

Osteoarthritis is eminently treatable in primary care with a number of management options for GPs, in addition to drug therapy. Glucosamine and chondroitin have few side effects and are worth recommending to patients with mild knee osteoarthritis.

Rheumatoid arthritis can cause significant disability, which can be limited by early diagnosis, referral, and treatment. Severe refractory rheumatoid arthritis may warrant referral for consideration of biologic therapy. Assessment of the cardiovascular risk and possible use of statins in rheumatoid patients may reduce their cardiovascular mortality.

GPs should aim to help patients to achieve optimum quality of life by using a holistic approach and by allowing maximum choice and control over their disease.

Introduction

Musculoskeletal disease is becoming more prevalent due to increased life expectancy and an ageing population. Primary care suffers the brunt of this increased workload and the aim of the Primary Care Rheumatology Society is to improve the quality of care to these patients by supporting and providing educational activities for all GPs.¹

This paper focuses on areas of musculoskeletal disease and rheumatology where recent advances in understanding and treatment have changed the management of these conditions; namely, osteoporosis, osteoarthritis, and rheumatoid arthritis.

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Osteoporosis

Osteoporosis is a progressive disease resulting in disabling fractures that cause substantial morbidity and mortality, impaired quality of life, and a massive socioeconomic burden (£1.7 billion costs in the United Kingdom [UK])² (Box 1).

Osteoporosis is most prevalent in postmenopausal women but, despite a 1 in 3 risk of developing osteoporosis during their lifetime, 80% of women do not feel that it will affect them personally³ and, therefore, education is vital.

The vertebral column is the most common site for osteoporotic fractures and these are associated with considerable morbidity and increased rates of mortality over 5 years.⁴⁻⁶ However, only a small proportion of vertebral fractures are presented clinically, and of the ones that are, only a proportion are detected by spinal imaging.⁶ Studies have shown that 50% of women have had at least one vertebral fracture by the age of 80-84 years, but only 15% have had a vertebral fracture clinically diagnosed.^{4,6-8}

Vertebral fractures are predictive of future fracture risk at the spine, hip, and, to a lesser extent, at all other sites; 20% of women will have another fracture within a year of a vertebral fracture incident.^{9,10} New vertebral fractures are associated with substantial increases in back pain and resulting functional disability in elderly women.¹¹ Prevention of new vertebral fractures should reduce the burden of back pain disability.

The hip is the second most common fracture site. There is a 1 in 6 lifetime risk of hip fractures for postmenopausal women, with the majority occurring in women over the age of 80 years.¹²⁻¹⁴ The morbidity and mortality of hip fractures is considerable, with 1 in 5 patients dying within 1 year of sustaining an osteoporotic fracture, and over 50% of patients remain permanently disabled with an impaired quality of life.^{15,16}

Identification of high-risk groups in primary care

A primary care audit found that most patients with an osteoporotic fracture had not been started on treatment,¹⁷ despite the availability of guidelines in primary care.^{18,19}

Population screening is not cost-effective, but identification and peripheral dual X-ray absorptiometry (DXA) of high-risk groups can identify 47% of osteoporotic patients at high risk of osteoporosis.²⁰ The standard high-risk groups include those patients with low body weight, kyphosis, family history of maternal hip fracture, early menopause, hyperthyroidism, glucocorticoid therapy, smokers, and those with a high alcohol intake.

- Osteoporosis is very common; affecting 1 in 3 women
- Every GP will have approximately 100 osteoporotic patients
- The most common osteoporotic fractures are vertebral and hip, both are associated with considerable morbidity and mortality
- 20% of hip fracture patients will die within a year, and 50% remain permanently disabled

Box 1. Key points for osteoporosis.

Bone loss with glucocorticoid therapy is greatest in the first 6 months of treatment, with fractures often occurring in the first 3 months. One in six patients taking >7.5 mg glucocorticoids daily have a vertebral fracture within a year. This has led the Royal College of Physicians to issue guidelines on the management of glucocorticoid-induced osteoporosis (Box 2).²¹

Although DXA of the hip and spine is the 'gold standard' for diagnosis of osteoporosis,²² it is not easily accessible or available in the UK. Screening in primary care using heel ultrasonography or peripheral DXA scan has been shown to have better specificity and predictive values compared with risk factor assessment, and can identify up to 90% of women with osteoporosis, which can be confirmed by axial DXA.²³⁻²⁷

Key points for the identification of high-risk groups are summarised in Box 3.

Prevention in primary care

Primary care plays a pivotal role in the provision of lifestyle advice throughout a patient's life, for example, regarding diet and exercise, and also in the education of patients and doctors in the management of established disease and in the prevention of falls. Lifestyle advice to patients for many chronic diseases has similar features, such as smoking cessation advice, reduction of alcohol intake, encouragement of aerobic exercise, and healthy diet advice, which also apply to osteoporosis. It is vital to coordinate the approach to offering a lifestyle message that encompasses all of the major diseases, including osteoporosis.

Falls are common in the elderly, with one person in two aged over 85 years and living at home falling at least once a year. Up to 10% of falls result in injury, usually a fracture, with consequent high morbidity and mortality.²⁸ Exercise programmes and home assessment to identify dangerous hazards such as loose carpets, and iatrogenic causes, such as multiple drug therapy, have been shown to reduce falls.

Hip protectors have been recommended but recent reviews have cast doubt on their effectiveness.²⁹⁻³¹ Exercise is important in the elderly and by increasing gait, balance, proprioception, reaction time, coordination, and muscle strength the risk of falls can be reduced.^{32,33} Exercise prevents osteoporosis by increasing bone mass, density and strength,^{34,35} and has its maximal effect if started at an early age. Adequate calcium intake is important at all ages but especially in children to ensure maximum bone mass is achieved before adult life, and in the elderly because malnutrition predisposes to falls.²⁸

A summary of key points for the prevention of osteoporosis is listed in Box 4.

Treatment in primary care

An adequate calcium intake (1000–1500 mg daily) is essential for postmenopausal women, by diet or supplements. In addition, 800 IU of vitamin D is recommended for house-bound elderly people because of the risk of subclinical vitamin D deficiency.

Although calcium and vitamin D alone are insufficient to treat established osteoporosis, their use in osteoporosis prevention, especially in elderly female nursing home residents, has been shown to be cost-effective.^{36,37} Calcium and vitamin D supplementation has also been shown to improve body

- For patients aged over 65 years, or with a previous fragility fracture, the risk of osteoporosis is high; therefore, advise general measures and start treatment
- Patients aged under 65 years without previous fragility fractures and who are starting oral glucocorticoids for more than 3 months should have their bone mineral density (T-score) measured using dual X-ray absorptiometry :
 - T-score over 0: reassure and advise general measures
 - T-score 0 to -1.5: general measures and repeat test in 1–3 years
 - T-score less than -1.5: treat for osteoporosis

Box 2. Royal College of Physicians' guidelines for the management of glucocorticoid-induced osteoporosis.²⁴

- Patients aged over 50 years with low fragility fractures should be offered treatment for osteoporosis
- Patients aged over 65 years starting steroids should have concomitant osteoporosis treatment
- Risk factor assessment identifies 50% of osteoporotic patients in primary care
- Risk factors include age, low body weight, loss of height, family history of maternal hip fracture, early menopause, smoking, high alcohol intake, and malabsorption problems
- Primary care screening of women aged over 65 years with heel ultrasonography or peripheral dual X-ray absorptiometry (DXA) can identify 90% of women with osteoporosis
- Axial DXA is still the 'gold standard' for diagnosis and is essential for monitoring treatment, but is not always available to primary care

Box 3. Identification of patients at high risk of osteoporosis.

- Unified lifestyle message required from primary care
- Prevention of falls in the elderly is a priority
- Hip protectors are of doubtful benefit
- Exercise not only increases bone mass and muscle strength but also improves gait, balance, and co-ordination
- Dietary advice needs to be targeted at all age groups, including the adolescents and the elderly

Box 4. Preventing osteoporosis.

sway and may therefore prevent falls and subsequent non-vertebral fractures in elderly women.³²

The bisphosphonates are now considered first-line treatment for postmenopausal osteoporosis and are anti-resorptive agents that reduce osteoclastic activity. Both alendronate and risedronate have excellent outcome data from large trials, which show that they significantly reduce the relative risk of vertebral and non-vertebral fractures by 40–50%.³⁸⁻⁴¹

In view of the recent evidence regarding the cardiovascular and thrombo-embolic risks of long-term hormone replacement therapy (HRT),⁴² guidelines have been issued by the Royal College of Physicians (Box 5).³⁸ They recommend that GPs should not prescribe HRT to asymptomatic women to prevent osteoporosis, because the risks outweigh the benefits even in women at high risk of osteoporosis.

In women with increased risk of breast cancer in whom HRT is contraindicated, the use of selective oestrogen receptor modulators (SERMs) has considerable benefit because of the dramatic reduction in risk of invasive breast cancer (76% during 3 years of treatment).⁴⁴

Gastrointestinal intolerance can be a problem with the use of bisphosphonate preparations, and once-weekly preparations

are better tolerated than daily preparations^{45,46} and aid compliance. There appears to be limited evidence for the long-term safety of these drugs over more than 12 years, and therefore it is difficult to commit patients to life-long treatment at present.

Key points for the treatment of osteoporosis are summarised in Box 6.

Advances in treatment

The development of teriparatide (recombinant human parathyroid hormone) is a major advance in osteoporosis treatment. It has a powerful effect on osteoblastic activity, which results in greater increases in bone mineral density compared with the bisphosphonates, and it reduces the relative fracture risk of vertebral and non-vertebral fractures by 50–65%.⁴⁷ It requires daily injections and, in view of its costs, will probably be restricted to the management of patients with severe osteoporotic cases in secondary care.

Another exciting area of research is in pro-osteoclastic cytokines, such as receptor-activating nuclear factor κ B ligand (RANKL), which binds to its receptor (RANK) on osteoclast precursors. Inhibition of RANKL results in prevention of bone loss and holds great promise in the future treatment of osteoporosis.⁴⁸

Strontium ranelate has been found to have osteoblastic as well as anti-osteoclastic activity, and has been shown to be a well tolerated oral therapy with significant increases in bone mineral density compared with placebo in trials so far.⁴⁹

Osteoarthritis

Osteoarthritis is the most common joint disorder in the world and the biggest single cause of disability.⁵⁰ In the UK, musculoskeletal problems account for about 25% of GPs' consultations, most of which are due to osteoarthritis.⁵¹ Fifty-four per cent of people aged over 65 years have osteoarthritis and 10% of the population aged over 50 years have osteoarthritis of the knees.⁵² The main aims of a GP treating patients with osteoarthritis are to reduce pain, optimise function, provide education and information, advise about prevention of further damage, and allay patients' fears and reassure them.

In addition to education, GPs can help osteoarthritic patients in a number of ways, including provision of aids, appliances, and orthoses, referral to other health professionals; for example, physiotherapists, podiatrists and occupational therapists, and use of drug treatment with topical preparations, analgesics, NSAIDs, and selective cyclo-oxygenase 2 inhibitors (coxibs), and with corticosteroid and hyaluronans injections.

Topical preparations

Application of creams can be useful if only one or two joints are involved. Capsaicin cream depletes the pain neurotransmitter, substance P, and apart from occasional stinging and burning, is usually well tolerated. Topical NSAID creams have been shown to be significantly more effective than placebo and have few adverse side effects.^{53,64}

Drug therapy

Paracetamol remains the first-line therapy in all age groups and, although it has been shown to be inferior to NSAIDs in the treatment of hip and knee pain caused by osteoarthritis,

- Hormone replacement therapy (HRT) should not be used to prevent or treat cardiovascular disease
- Women requiring HRT for menopausal symptoms should have their coronary heart disease risk assessed
- HRT is not recommended as first-line therapy for prevention and treatment of osteoporosis, except for women needing treatment for menopausal symptoms
- Treatment should be assessed annually
- Women with early menopause should take HRT up to the age of 50 years

Box 5. Royal College of Physicians guidelines for hormone replacement therapy.⁴³

- Patients in residential nursing homes will benefit from calcium and vitamin D supplementation
- Vitamin D has other benefits for neuromuscular coordination that may reduce the risk of falls
- Bisphosphonates are the first-line treatment and once-weekly preparations improve tolerability and aid compliance
- Hormone replacement therapy (HRT) is no longer an initial choice for osteoporosis treatment
- Selective oestrogen receptor modulators may be a useful alternative in postmenopausal women where HRT is contraindicated
- Treatment needs to be focused on the highest risk group — the elderly

Box 6. Treatment of osteoporosis in primary care.

both drugs have similar benefits in terms of functional improvement.⁵⁵

Non-steroidal anti-inflammatory drugs

NSAIDs are used extensively worldwide and most doctors are now aware of the risks of gastrointestinal toxicity. For every 1200 patients taking NSAIDs for at least 2 months, one will die from gastroduodenal complications as a result of NSAID treatment.⁵⁶ In order to reduce these risks, patients should take the lowest dose of NSAID for the shortest duration, be aware that risks are highest in the elderly, make sure that the combination of aspirin and an NSAID is avoided if possible, and they should be aware that all NSAIDs, including ibuprofen and coxibs, have been associated with serious and fatal gastrointestinal reactions. The cardioprotective effects of low-dose aspirin may be compromised by co-prescribing NSAIDs, but not by the intermittent use of NSAIDs.

A nurse-based advice intervention reduced chronic NSAID use in primary care, with 28% more patients in the intervention group either stopping NSAIDs or reducing the dosage by at least 50% compared with the control group.⁵⁷

What about coxibs? NSAIDs are associated with gastric mucosal injury that may result in peptic ulceration, upper gastrointestinal haemorrhage, and perforation.⁵⁸ Mucosal injury is thought to be mainly due to the inhibition of prostaglandins by NSAIDs. Prostaglandin synthesis is catalysed by two cyclo-oxygenase enzymes. Most NSAIDs are nonselective and inhibit the activity of the COX 1 enzyme in the stomach as much as the COX 2 enzyme, which is induced in the inflamed synovium. Prostaglandin synthesis stimulates the mucosal defence mechanisms and COX 1 inhibition results in the gastrointestinal complications of NSAIDs.⁵⁹ Coxibs have been developed that have selective COX 2 activity and provide the

- Patients aged over 65 years
- Prior history of ulcers or gastrointestinal complications
- Use of steroids or anticoagulants
- Serious comorbidity
- Requirement for prolonged use of maximal doses.

Box 7. National Institute for Clinical Excellence recommendations on the use of coxibs.

powerful anti-inflammatory action of standard NSAIDs with reduced gastrointestinal toxicity.

All coxibs have equivalent efficacy to NSAIDs in full dosage and may have a longer duration of action.⁶⁰ Four large studies have analysed the gastrointestinal safety of rofecoxib and celecoxib in over 39 000 patients with osteoarthritis or rheumatoid arthritis.⁶¹⁻⁶⁴ The results have shown that patients taking rofecoxib and celecoxib had significantly lower rates of gastrointestinal adverse events than those taking nonselective NSAIDs. Patients with multiple risk factors or who were taking low dose aspirin and corticosteroids as well as a coxib had a reduced risk of upper gastrointestinal events.

When should GPs use coxibs? The improved gastrointestinal profile of coxibs has led the National Institute for Clinical Excellence to issue recommendations on their usage (Box 7). Although coxibs have a better safety profile than NSAIDs, 30–40% of patients will still need their medication changed within 6–12 months for some reason; for example, lack of efficacy.⁶⁵

Cost-effectiveness of coxibs is related not only to a decrease in serious gastrointestinal events treated in secondary care, but also to the reduction in co-prescribing of gastroprotective agents with coxibs compared with NSAIDs.⁶⁶

Apart from gastrointestinal safety, are coxibs safer? All NSAIDs can affect blood pressure significantly — both standard NSAIDs and coxibs.⁶⁷ NSAIDs, including coxibs can impair renal function and result in water and sodium retention in susceptible individuals, and they have been implicated in nearly 20% of hospital admissions with heart failure. The use of NSAIDs, including coxibs, should be avoided in patients with heart failure. If treatment is unavoidable, education of patients and careful monitoring is essential.^{68,69}

Key points for the treatment of osteoarthritis with NSAIDs are summarised in Box 8.

Viscosupplementation

Three to five intra-articular injections of hyaluronic acid into an osteoarthritic knee at weekly intervals have been shown to provide pain relief and functional improvements for up to 6 months.⁷⁰⁻⁷² Viscosupplementation may have a place in the treatment of patients with mild to moderate knee osteoarthritis who cannot tolerate corticosteroids, or in patients waiting for total knee replacement. There is little evidence on the long-term benefits and safety of viscosupplementation.⁷³

Corticosteroid injections are widely used, cost-effective and provide immediate benefits to patients, although long-term outcomes show little difference from other treatments, such as physiotherapy.

Although most authorities recommend no more than 3 or 4 injections a year, a recent study has confirmed the safety

- Paracetamol remains the initial choice of therapy
- All NSAIDs have gastrointestinal toxicity related to their COX 1 activity
- Use the lowest dose of NSAID for the shortest time
- For patients requiring long-term NSAIDs:
 - Consider checking *Helicobacter pylori* status and possible treatment prior to starting NSAIDs
 - Follow NICE guidelines for coxibs, which are equally efficacious and have a better safety profile
 - Avoid NSAID and coxib treatment, if possible, for: (a) patients on low-dose aspirin, (b) patients with hypertension, and (c) elderly patients, at risk of heart failure

Box 8. Key points for the use of non-steroidal anti-inflammatory drugs.

of repeated corticosteroid injection for knee osteoarthritis.⁷⁴ In addition to the anti-inflammatory benefits of corticosteroids, joint aspiration is useful for diagnostic purposes to exclude sepsis and crystal arthropathies, as well as to relieve the pressure of a tense effusion.

Patellar taping of the knee in patients with patellofemoral osteoarthritis has been shown to reduce knee pain and self-reported disability significantly, and is a cheap and effective method of pain relief that can be taught to patients by a physiotherapist.⁷⁵ Patients with knee osteoarthritis have reported pain reduction of up to 50% immediately after tape application. These benefits can be maintained in the short term after treatment has been stopped.^{76,77}

Glucosamine/chondroitin

Glucosamine, a naturally occurring aminoglycoside, is a precursor of the glycosaminoglycans, an important constituent of articular cartilage. *In vitro* studies support its role in cartilage repair by stimulating synthesis of glycosaminoglycans.

A Cochrane review concluded that glucosamine had a clinical effect equivalent to NSAIDs and had a significantly better result than placebo, with an excellent side-effect profile.⁷⁸ Another review, a meta-analysis of placebo-controlled trials, again found in favour of a beneficial effect of both glucosamine and chondroitin in pain relief, and functional improvement in patients with knee osteoarthritis.⁷⁹ Two recent studies have shown that significant joint space narrowing in knee osteoarthritis occurs to a much lesser degree in patients on glucosamine compared with placebo.^{80,81} More long-term studies are needed to confirm these findings. The consensus of the experts is that glucosamine and chondroitin are safe and cheap, with a possible equivalent efficacy to NSAIDs in the long term (at least a month), and are therefore worth recommending to patients with mild to moderate knee osteoarthritis.⁸²

As yet there is no standardisation of over-the-counter preparations, although the recommended dosage of glucosamine is 1500 mg daily.

Exercise

There is extensive literature that supports the benefits of exercise in the osteoarthritic patient, especially for knee osteoarthritis,^{83,84} but it is still an underused therapeutic intervention due to barriers such as patients' lack of knowledge about its benefit, attitudes about the appropriateness of

- The benefits of exercise in osteoarthritis cannot be stressed enough
- Glucosamine/chondroitin supplementation appears to be a safe and effective treatment available over the counter, for osteoarthritic knee and may slow down disease progression
- Patellar taping is a useful cost-effective method of pain relief for osteoarthritic knee
- Corticosteroid and hyaluronic acid injections have a place in the short-term relief of pain and functional impairment of osteoarthritic knee

Box 9. Key treatments for knee osteoarthritis.

exercise in the elderly, and adverse environmental factors that limit exercise uptake.⁸⁵ It is important that GPs take these factors into account in order to tailor exercise regimes to the individual. Numerous successful schemes in the UK (exercise on prescription, for example) are active and, not only provide mutual support, but allow the individual to start at the appropriate level of exercise.

Advances in knowledge of osteoarthritis

Our knowledge of the pathogenesis of osteoarthritis has advanced through our understanding of the microanatomy and physiology of articular cartilage. Articular cartilage has always been thought of as an inert lubricating layer between joints, but we now know that there is an active process of degradation and repair, and that chondrocyte metabolism is activated by physiological and pathological mechanical loads.

Articular cartilage is comprised of a collagen network, made up of chains of protein molecules, supported by a matrix of very large complex molecules called aggrecans whose three-dimensional shape enables them to retain water and gives shape, elasticity, and strength to the cartilage. Aggrecans are comprised of proteoglycans, which themselves are made from many glycosaminoglycans molecules joined together by hyaluronic acid.

Matrix metalloproteinases (MMPs) are proteolytic enzymes that are involved in constant active matrix breakdown and replacement, which helps to maintain tissue integrity. If degradation exceeds renewal then the impaired collagen network leads to surface fibrillations which are the initial stage in the progression to osteoarthritis. Further progression may depend on the mechanical load on the joint. Excessive expression of MMPs is known to occur in osteoarthritis and, therefore, there is much interest in the possible use of MMP inhibitors, which could prevent cartilage breakdown at an early stage before progression to osteoarthritis.⁸⁶⁻⁸⁸

The other main area of research is in the involvement of the cytokine pathways that are activated in osteoarthritis and lead to synovial inflammation. Some cytokines, notably interleukin-1 (IL-1) and tumour necrosis factor- α (TNF- α) are produced by the synovium and up-regulate MMPs. Inhibition of these cytokines may be of benefit in preventing progression in osteoarthritis.⁸⁹

What does the future hold for NSAIDs and coxibs?

Nitrogen oxide-releasing NSAIDs (NO-NSAIDs) are derived from standard NSAIDs and are able to release nitric oxide over

a long period of time. They have a good anti-inflammatory effect with minimal gastrointestinal and cardiovascular/renal toxicity.⁹⁰

NSAIDs have been shown to have beneficial effects in the inhibition of colorectal carcinogenesis and possibly Alzheimer's disease, and large-scale trials for both are currently under way.^{91,92}

Key points for the treatment of knee osteoarthritis are summarised in Box 9.

Rheumatoid arthritis

Rheumatoid arthritis is a chronic, progressive disease that affects 1 in 100 of the total UK population,⁵² and causes joint pain and stiffness that can often lead to considerable loss of function with consequent disability.

The initial priority with rheumatoid arthritis is to make the diagnosis and referral early in onset. Despite guidelines,⁹³ there is still considerable delay before many patients have a diagnosis and are started on disease-modifying drugs.⁹⁴

Diagnosis can be very difficult in the early stages, with patients complaining of non-specific, vague, systemic symptoms, little active synovitis, and with no reliable diagnostic tests available. GPs also have to consider the differential diagnoses of viral arthralgia, osteoarthritis, and other seronegative arthropathies. Diagnosis of rheumatoid arthritis is easier when the classic symptoms and signs are present (Box 10).⁹⁵ In addition to starting disease-modifying drugs at an early stage, early intervention allows assessment by the multidisciplinary team and education of patients to help them to cope with their disease.

The main aims of treatment are to control joint pain and swelling, reduce permanent joint damage, prevent loss of function and disability, and to enable patients to gain control of their disease and improve the quality of their life using a holistic approach.

Disease-modifying drugs not only improve the symptoms and reduce the inflammatory markers of rheumatoid arthritis, they also halt disease progression and minimise irreversible joint damage, resulting in improved outcome measures, quality of life, and disability.⁹⁶ Unfortunately, disease-modifying drugs give a suboptimal response in some patients and they are also limited in efficacy by their toxicity, which results in many patients either failing to respond adequately or having to stop treatment because of side effects.

Biologic therapy

For patients who have failed to respond to disease-modifying drugs, the development of the new biologics, the anti-TNF- α

At least four of these signs or symptoms present for 6 weeks:

- Pain and swelling in at least three joint areas
- Symmetrical presentation
- Early morning joint stiffness for more than 1 hour
- Involvement of metacarpophalangeal joints or proximal interphalangeal joints or wrists
- Subcutaneous nodules
- Positive rheumatoid factor
- Radiological evidence of erosions

Box 10. Symptoms and signs of rheumatoid arthritis.⁹⁵

drugs, represent a major advance in the treatment of rheumatoid arthritis. These biologic drugs work by switching off the cytokine, TNF- α , which stimulates cells to produce the inflammatory response that results in the synovitis of painful swollen joints.

Three biological molecules have been developed: etanercept and infliximab (licensed for treatment in the UK), and adalimumab. Etanercept is a recombinant human TNF receptor fusion protein, which binds to circulating or cell-bound TNF molecules and blocks the action of TNF- α . It has to be given subcutaneously twice weekly. Infliximab is a chimeric murine/human anti-TNF monoclonal antibody, which binds to soluble as well as membrane-bound TNF and neutralises the effect of TNF- α . It has to be given by slow intravenous infusion at 0, 2, and 6 weeks and then 8-weekly intervals, and is used in combination with methotrexate. Adalimumab is a fully human anti-TNF monoclonal antibody and is given subcutaneously on alternate weeks. They all have a very rapid onset of action, with the majority of patients achieving a clinically significant response within the first 2 weeks of treatment.⁹⁷⁻⁹⁹

Patients' quality of life has been shown to be substantially improved, with a significant reduction in health assessment questionnaire (HAQ) scores with all of the anti-TNF drugs. They have all been shown to prevent radiographic progression of the disease, as well as sustained efficacy over 4 years associated with a lack of major toxicity.^{100,101}

NICE guidelines recommend the use of etanercept and infliximab (the latter only in combination with methotrexate) as options for the treatment of adults who have continuing active rheumatoid arthritis that has not responded adequately to at least two disease-modifying drugs, including methotrexate (unless contraindicated).¹⁰²

Toxicity of these drugs is very low and in general they are well tolerated. Injection site reactions have occurred with etanercept, and infusion-related side effects; for example, dyspnoea, fever, and urticaria, have been reported with infliximab. There were no increases in the incidence of infections, serious or otherwise, during the clinical trials and long-term follow-up, but a number of cases of reactivation of tuberculosis have been reported with infliximab. There is a theoretical risk of malignancy, and data suggests that there may be an increased risk of lymphoma in rheumatoid arthritis patients treated with anti-TNF drugs, but at present this is difficult to quantify because of confounding factors.¹⁰³

Anti-TNF drugs have been shown to be highly effective in rheumatoid arthritis, with a rapid action, good risk-benefit ratio, and a sustainable response over 4 years, and deserve to be more widely available in the UK.¹⁰⁴ The high initial drug costs are offset by the long-term socioeconomic savings produced by the prevention of disease progression.

Advances in treatment

Anakinra is the first interleukin antagonist available in the UK. IL-1 is an important proinflammatory cytokine which is involved in the pathophysiology of rheumatoid arthritis. Anakinra is a recombinant IL-1 antagonist that produces a significant improvement in symptoms of patients with rheumatoid arthritis, reduces radiological disease progres-

- Check rheumatoid arthritis patients for cardiovascular risk factors, especially blood pressure and lipids
- Be aware of the effect of non-steroidal anti-inflammatory drugs (NSAIDs) on blood pressure, and reduce dose if possible
- Do not stop aspirin for cardiovascular protection, even if patients are on NSAIDs or coxibs, but try and use NSAIDs intermittently to avoid compromising the effectiveness of the aspirin
- Avoid use of angiotensin converting enzyme inhibitors with NSAIDs, especially in the elderly
- Consider the use of statins in rheumatoid arthritis
- Encourage exercise

Box 11. Treatment of rheumatoid arthritis and cardiovascular disease.

sion, and improves quality of life as measured by the HAQ. It has a favourable risk-benefit profile.¹⁰⁵⁻¹⁰⁷

Anti-TNF- α drugs are showing great promise in the treatment of other autoimmune diseases in addition to rheumatoid arthritis, particularly, in sero-negative arthropathies such as ankylosing spondylitis and psoriasis.^{108,109}

Rheumatoid arthritis and cardiovascular disease

Despite these advances in treatment, the mortality of rheumatoid arthritis does not appear to have altered over the last 30 years. Rheumatoid arthritis is associated with a significantly increased risk of cardiovascular disease resulting in increased comorbidity and mortality.¹¹⁰ The risk is similar to that associated with type 2 diabetes, and accounts for almost half of all deaths in patients with rheumatoid arthritis. In severe rheumatoid arthritis, the risk is equivalent to that from triple vessel coronary disease. This appears to be mainly due to ischaemic heart disease.¹¹¹ There is evidence that endothelial dysfunction, secondary to rheumatoid vasculitis, results in accelerated atherogenesis.¹¹² Hypertension is common in patients with rheumatoid arthritis and is significantly increased by NSAIDs and coxibs. GPs should be aware that using angiotensin converting enzyme (ACE) inhibitors in patients taking NSAIDs may lead to nephrotoxicity.¹¹³ Abnormal lipid profiles are common in patients with rheumatoid arthritis, and active rheumatoid arthritis is associated with reduction in high-density lipoprotein.

The use of statins has been shown to improve the lipid profile and reduce cardiovascular disease in general, and their use in rheumatoid arthritis treatment may not only reduce cardiovascular risks but may also have a beneficial immunomodulatory and anti-inflammatory function on rheumatoid arthritis disease activity.¹¹⁴

Key points for the treatment of rheumatoid arthritis and cardiovascular disease are summarised in Box 11.

Self-management

Encouraging patients to manage their own disease is a vital part of treatment. GPs have a critical role in helping, not only with all aspects of chronic disease management, but also with educational activities and directing patients to other sources of information and support, such as the arthritis charities. Despite all of these advances in musculoskeletal medicine, GPs need to retain a holistic approach to allow the individual to retain full control of their disease and ensure optimum quality of life.

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